Dissertation

Title of project

An audit of compliance to referral criteria for patients with suspected renovascular hypertension referred for angiotensin converting enzyme inhibitor study at Dr George Mukhari Academic Hospital.

By

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Research protocol

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DECLARATION

I declare that the dissertation hereby submitted to Sefako Makgatho University, for the degree of Master of Medicine (MMed) in Nuclear Medicine has not previously been submitted by me for a degree at this or any other University; that it is my work in design and in execution, and that all materials contained herein has been duly acknowledged.

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Student Number:  
Date


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DEDICATION

This dissertation is dedicated to my late father Mr. Nemutaduni Makungo, my loving husband, my children, my mother, my parents in law, my sister, aunty and the rest of my family at large. Thank you for being the pillar of strength, for taking good care of my children when I could not give them my undivided attention, but this however was never going to be possible without God who gave me the strength to go on even when it seemed humanly impossible to complete the task.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A-II</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>ACEI</td>
<td>Angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>ARD</td>
<td>Atherosclerotic renovascular disease</td>
</tr>
<tr>
<td>CC</td>
<td>Cisterna chyle</td>
</tr>
<tr>
<td>CTPA</td>
<td>Computed tomographic angiography</td>
</tr>
<tr>
<td>DTPA</td>
<td>Diethylene- triamine- penta acetic acid</td>
</tr>
<tr>
<td>DSA</td>
<td>Digital subtraction angiogram</td>
</tr>
<tr>
<td>DGMAH</td>
<td>Dr George Mukhari Academic Hospital</td>
</tr>
<tr>
<td>EJNM</td>
<td>European Journal of Nuclear Medicine</td>
</tr>
<tr>
<td>FMD</td>
<td>Fibromuscular dysplasia</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HT</td>
<td>Hypertension</td>
</tr>
<tr>
<td>I.V</td>
<td>Intravenous</td>
</tr>
<tr>
<td>JG</td>
<td>Juxta-glomerular</td>
</tr>
<tr>
<td>L/N</td>
<td>Lymph node</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MAG3</td>
<td>Mercapto-acetyl triglicine</td>
</tr>
<tr>
<td>RP</td>
<td>Radiopharmaceuticals</td>
</tr>
<tr>
<td>RAS</td>
<td>Renal artery stenosis</td>
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<tr>
<td>RI</td>
<td>Resistance index</td>
</tr>
<tr>
<td>RVH</td>
<td>Renovascular hypertension</td>
</tr>
<tr>
<td>TPR</td>
<td>Total peripheral resistance</td>
</tr>
<tr>
<td>TAC</td>
<td>Time activity curve</td>
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<td>U/S</td>
<td>Ultra-sound</td>
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Background:

Renovascular hypertension (RVH) affects 1-5% of the unselected hypertensive population. An angiotensin converting enzyme inhibitor (ACEI) augmented radionuclide renography scan may be performed in order to diagnose RVH as a consequence of renal artery stenosis. It assesses activation of the RAS (renin angiotensin system) as a sequelae of RVH. A positive exam predicts better control or normalisation of blood pressure following revascularisation but an ACEI-augmented renography test is cost effective if used only in patients with moderate to high risk of RVH. The European Association of Nuclear Medicine (EANM) procedure guidelines function as a vehicle that assists nuclear medicine physicians in recommending, performing and interpreting the renal scintigraphy in the diagnosis of RVH.

Aim:

This study aimed at determining the level of compliance of referring physicians to the EANM guidelines for ACEI-augmented renal scintigraphy in patients with suspected RVH in order to predict curability of hypertension following intervention.

Methods:

The files of 140 patients were retrospectively evaluated. Compliance to referral criteria was analysed. The severity of hypertension, the age at which patients presented with hypertension and target organ damage were assessed from the data of each patient’s clinical file and correlated to the results of the ACEI-augmented renography.

Results:

A total of 140 patients were studied. The age range of the patients was 3-82 years with a mean age of 30.19 years. The study revealed that a large number of patients (41%) referred with a presumptive diagnosis of RVH were younger than 30 years of age and complied with one of the EANM criteria, but also that 30% of them did not meet any of the criteria. Among the patients presenting with a positive ACEI-augmented renography, the majority (60%) presented with severely elevated blood pressure (systolic blood pressure of more than 160 mmHg and diastolic blood pressure of more than 100 mmHg).
Tc-99m diethylene-triamine penta acetic acid (DTPA) was the more commonly used radiopharmaceutical (70% of the patients) and detected a majority of the positive cases (80%) as per criteria. Tc-99m mercaptoacetyl triglycine (MAG3) was used in 30% of the patients and detected 20% of the positive cases (as per criteria).

**Conclusion:**

This retrospective audit highlights that the majority of patients with suspected RVH and referred for ACEI-augmented renal scintigraphy at Dr George Mukhari Academic Hospital were not adequately pre-selected for the study. Although the results are not statistically significant, they highlight that the EANM guidelines were not adhered to by referring physicians with respect to patients with suspected RVH, leading to the unnecessary cost and radiation exposure to the scan; and accounting for the large number of negative studies. We recommend the following measures to address the outcomes: (1) institution of a vetting form for ACEI-augmented scans, (2) development of a referral protocol to assist physicians in imaging patients with suspected RVH and (3) continuous medical education to referral base.
CHAPTER 1

INTRODUCTION

This chapter gives an overview of the research project that includes the background of the study, the problem statement and the importance of conducting a study of this kind.

1.1 RATIONALE OF THE STUDY

The purpose of this retrospective study was to conduct an audit on the appropriateness of referral of patients that underwent angiotensin converting enzyme inhibitor (ACEI) augmented radionuclide renal scintigraphy at Dr George Mukhari Academic Hospital (DGMAH). ACEI-augmented renal scintigraphy is more cost effective and appropriate when performed in patients with suspected renovascular hypertension (RVH) as diagnosed by criteria published in various guidelines, such as those advocated by the EANM. Subjectively, a large percentage of negative ACEI renal scans at the department of Nuclear Medicine (DNM) was noted, which led to the question: do referring physicians adhere to the referral criteria when requesting ACEI renal studies in patients with suspected RVH?

1.2 BACKGROUND OF THE STUDY AND LITERATURE REVIEW

1.2.1 Hypertension

According to the American Heart Association, hypertension (HT) is defined as systolic blood pressure (SBP) of 130 mmHg or more and/or diastolic blood pressure (DBP) of 90 mmHg or more in adults. In children between the ages of 3 and 12 years, abnormal blood pressure (BP) is considered when the SBP is more than 106 mmHg and the DBP is more than 63 mmHg. HT is comprehensively one of the most common diseases and is a major risk factor for stroke, myocardial infarction, vascular disease and chronic renal disease. The aetiology of most cases of HT in adults is still unknown and control of BP is suboptimal in the general population. Hypertension may be characterised as either primary or secondary. Primary HT is diagnosed when a secondary cause cannot be identified and accounts for 90-95% of adults with HT. Secondary HT is due to an underlying pathology and accounts for 5-10% of cases. Common causes of secondary hypertension are listed in Table 1.1 below. The importance of diagnosing a secondary cause is potential cure or better control of the HT with treatment of the underlying pathology.
1. Endocrine causes
   Cushing’s syndrome
   Conn’s syndrome
   Phaeochromocytoma
   Hyperparathyroidism

2. Renal causes
   Renal artery stenosis
   Diabetic neuropathy
   Glomerulonephritis

3. Other causes
   Coarctation of the aorta
   Alcohol
   Pregnancy-associated hypertension
   Stress
   Sleep apnoea

Table 1.1 Common causes of secondary hypertension

Among the causes of secondary HT is RVH, which is defined as elevated BP caused by renal hypo-perfusion, usually resulting from anatomical stenosis of the renal artery and inappropriate activation of the renin angiotensin system, which in turn results in systemic HT.\(^{4}\)

1.2.2.1 Renin angiotensin system and RVH

The renin angiotensin system is a protective physiologic mechanism to maintain kidney perfusion and glomerular filtration in the setting of low systemic blood pressure.

It is inappropriately activated in the setting of renal artery stenosis (RAS) where renal hypo-perfusion results from reduced blood flow through a narrowed vessel rather than low SBP. The kidney responds to the post-stenotic low renal arterial perfusion by releasing the hormone renin from the juxtaglomerular apparatus, which is situated in close proximity to the macula densa.\(^{5,6}\)
Renin converts angiotensinogen in the liver to angiotensin I, which is in turn converted to vasoactive angiotensin II (A-II) by angiotensin converting enzyme (ACE) in the lungs.\(^7\)

A-II maintains the glomerular filtration rate (GFR) by vasoconstriction of the efferent arteriole of the renal glomerulus, thus increasing the trans-glomerular hydrostatic pressure and GFR. A-II also increases SBP by two mechanisms: (1) it acts as a vasoconstrictor peripherally to increase total peripheral resistance (TPR) and (2) it stimulates the production of aldosterone in the adrenal cortex, which in turn stimulates sodium and water reabsorption in the distal intra-renal tubules, resulting in increased blood volume and also cardiac output (CO) as a result of Franck-Starling law. With TPR and CO being respectively increased by the aforementioned mechanisms, and with BP= TPR x CO, these mechanisms increase systemic BP and result in RVH.\(^8,9\)

RVH affects 1-5% percent of patients with hypertension and this percentage increases with age.\(^10\) RVH is the most common cause of secondary HT.\(^11\)

Despite the relatively small number of patients, RVH continues to provoke considerable clinical and theoretical interest because it is potentially curable. Re-establishment of normal renal perfusion results in the deactivation of the renin angiotensin system and BP is either normalised or becomes easier to manage. For the very young, it might mean relief from unnecessary anti-HT drugs and for the elderly it may mean elimination of drugs that are often poorly tolerated due to their age.\(^12,13\) Although RVH may have a variety of causes, by far the most common aetiology is RAS caused by either atherosclerosis or fibro muscular dysplasia (FMD). Atherosclerotic renovascular disease (ARD) usually occurs in patients in the fifth through seventh decade but is occasionally found in younger patients. It is believed that 90% of all renal lesions are due to atherosclerosis, making it the most common cause of RVH. It is far more prevalent in males than in females, with a ratio of two to one. The risk factors for development of ARD include age, HT, smoking, hyperlipidaemia, diabetes and renal failure.\(^14,15\)

FMD is considered to be the most common cause of RVH in patients under the age of 40 years, accounting for 10% of all cases of RAS. It is characterised by regularly arranged sub-endothelial mesenchymal cells within a loose matrix of fibrous connective tissue.\(^16\) It produces fibromuscular ridges which bring about alternating stenosis and dilatation of the artery, resulting in the classic ‘string beads’ appearance on angiography, located in the distal two thirds of the main renal artery.\(^17\) In the pathogenesis of FMD, female hormones are
likely to be implicated in view of the large female predominance; a few cases occur in familial autosomal dominant pattern and also in association with alpha 1 anti-trypsin deficiency. Pathology includes two main types: intimal fibroplasia, which is defined as accumulation of non-atherosclerotic and non-inflammatory fibrous tissue in the intima and affects women in their fourth decade; and peri-medial fibroplasia, which is a form of FMD wherein fibrous tissue replaces the outer portion of medial muscle layer, leading to stenosis.\(^{(18)}\)

1.2.3 Angiotensin converting enzyme inhibitor-augmented renography

The main goal of the ACEI-augmented renal scintigraphy is to detect those patients who have HT as a consequence of unilateral RAS; the test detects patients whose kidney function may drop after the introduction of ACEI, indicating potential curability or improvement in HT control after intervention.\(^{(18, 19)}\)

ACEI-augmented renography is a sensitive, non-invasive functional method for diagnosing RVH.\(^{(20)}\) ACEI works by blocking the conversion of angiotensin I to angiotensin II, which causes (GFR) to fall in patients with RVH who rely on compensatory mechanisms to maintain perfusion pressure.\(^{(21, 22)}\) The study is performed in two phases: a ‘baseline’ scan is performed and then compared to subsequent study where ACEI is administered to the patient – the aforementioned drop in GFR is demonstrated as deterioration of function of the affected kidney on the ACEI scan as compared to the baseline study.\(^{(23)}\)

Dondi et al. postulate that ACEI renography is best indicated in cases of moderate to severe HT in patients who are resistant to therapy and presenting with unilateral renal artery stenosis. ACEI-augmented renography is therefore not really a test for primary detection of RAS, but rather a second line investigation to detect inappropriate activation of the RAS in a patient with US or CT evidence of a narrowed renal artery; the aim being to determine if the narrowed artery is the cause of the HT, or a consequence of the HT (a complication of chronically elevated blood pressure is the development of arterial narrowing). RVH is considered to be a retrospective diagnosis viz. only with normalisation or better control of the HT following revascularization, can RVH be established.\(^{(24)}\)

The test is more sensitive and cost effective if used primarily in patients who have a moderate to high risk of RVH, as assessed by a number of clinical features. The risk factors associated
with RVH as defined by the European Association of Nuclear Medicine (EANM) guidelines include: \(^{(3, 19)}\)

- Hypertension that is resistant to drug therapy in a compliant patient.
- Onset of hypertension before age 30 or after age 55.
- Sudden onset of severe hypertension.
- Abdominal or flank bruits.
- Worsening renal function during anti-hypertensive therapy, especially ACEI or angiotensin II receptor blocker.
- Grade 3 or 4 hypertensive retinopathy.
- Occlusive disease in other vascular beds.
- Recurrent pulmonary oedema in elderly hypertensive patients.
- Hypertension in infants with an umbilical artery catheter.
- Hypertension in children.

### 1.3 RESEARCH QUESTION

Is there compliance and adherence to the referral criteria for ACEI-augmented renal scintigraphy in patients with suspected RVH at DGMAH?

### 1.4 RESEARCH AIM AND OBJECTIVES

The overall aim of the study was to determine the compliance of referring physicians to the referral criteria for ACEI-augmented renal scintigraphy study in patients with suspected RVH.

The objectives of the study were as follows:

- To analyse the reasons for referral for ACEI-augmented renal scintigraphy.
- To determine the appropriateness of the referrals and compliance to the EANM criteria.
CHAPTER 2
THEORETICAL FRAMEWORK AND LITERATURE REVIEW

This chapter gives an overview of the theoretical framework of disease related to the kidneys, with an emphasis on RVH and ACEI renography.

2.1 INTRODUCTION: RENOVASCULAR HYPERTENSION

RVH is defined as a form of secondary HT resulting from renal arterial compromise, which is usually due to obstruction of the main renal artery.\textsuperscript{(25)} It is more commonly diagnosed in elderly patients. Sequentially, it may start as asymptomatic RAS and undetected and untreated, may progress to ischaemic nephropathy and other complications such as congestive cardiac disease and stroke.\textsuperscript{(26)}

2.1.1 Epidemiology and prevalence

RVH is the most common and curable form of secondary HT. It is found in 1-5\% of unselected hypertension patients and in 30\% of selected patients with secondary hypertension. It is relatively uncommon in patients with mild hypertension.\textsuperscript{(11, 12, 20, 27)}

RAS resulting from atherosclerotic disease is commonly found in individuals undergoing coronary angiography. Atherosclerotic disease is the predominant cause of renal lesions detected in patients of over 50 years of age. The majority of patients have silent RVD, which makes it challenging to accurately assess the prevalence of the disease. RVD may be associated with HT and heart failure.\textsuperscript{(27, 28, 29, 30)}

2.2 RENAL ANATOMY

2.2.1 DEVELOPMENTAL ANATOMY OF THE KIDNEYS

Three main structures develop during the development of the kidneys - the pronephros, mesonephros and metanephros. The pronephros develops during the fourth embryonic week and, by birth, all signs of the pronephros have disappeared. The S-shaped tubules from the pronephros become the glomerulus and tubules around the glomerulus forms Bowman’s capsule.\textsuperscript{(31, 32)}

In both sexes, the ureters, renal pelvis and bladder trigone originate from the mesonephric duct; it also gives rise to the vasa differentia and seminal vesicles.\textsuperscript{(33)}
2.2.2 GROSS ANATOMY OF THE KIDNEYS

The kidneys are bean-shaped structures that weigh about 150g in males and 135g in females, which amounts to roughly the size of a fist. Two regions are seen: an outer part called the cortex and an inner medulla. The cut surface of a bisected kidney show a pale outer region, the cortex and a darker region called the medulla. The medulla is divided into 8-18 striated cortical masses called the renal pyramids and the base of the pyramids is positioned at the cortico-medullary boundary to form a papilla. The small opening at the tip of the papilla forms the collecting duct. (34)

The renal cortex appears as a cap over the base of each pyramid and it is 1cm thick. It extends downwards between the pyramids and forms the column of bertin. The renal pelvis forms part of the extended portion of the urinary tract. The major calyces extend outwards from the upper dilated end of the renal pelvis and several minor calyces extend towards the papillae of the pyramids to drain the urine formed by each pyramid. (35)

2.2.3 BLOOD SUPPLY OF THE KIDNEYS

The blood supply from the kidneys arises from the abdominal aorta at the level of the L2 vertebrae and before it reaches each kidney, it divides into segmental arteries which are responsible for nourishing the various parts of the kidneys. The renal veins are responsible for draining blood from the venules arising from interlobar capillaries from the renal parenchyma; both eventually drain into the inferior vena cava. (36)

The anatomical distribution of lymphatic drainage of the kidneys varies from person to person. The kidney lymphatic vessels are mostly arranged in three parts: peri-renal fat vessels, vessels under renal capsule and para-tubular vessels. These join together to form a trunk which runs along the renal vein to the lateral aortic nodes and the para-aortic lymph node located in the left crura of the diaphragm. The efferent vessel then drains into the lumbar lymph trunk, which forms the cisterna chyle (CC). CC ultimately drains into the thoracic duct. The outflow is only via the renal cortex and not the medulla. (37, 38)

2.3 PHYSIOLOGY OF THE KIDNEYS

Both kidneys receive around 20% of the oxygenated blood from cardiac output for filtration purposes. Glomerular capillaries are branches of the afferent arteries. The efferent arteriole diverts blood away from the glomerular capillaries into the interlobar capillaries, which are
responsible for oxygenation of the kidneys. The plasma enters the glomeruli through the Bowman’s space. (39)

The kidneys have an important role, which involves filtering circulating blood in order to maintain fluid and water balance of the body by continual filtration of the blood through the three main processes of glomerular filtration, tubular secretion and tubular reabsorption. (40)

The second critical task is the management of extracellular fluid, circulating blood volumes and regulation of blood pressure. Specialised distal tubule cells located in the afferent arteriole, known as the macula densa, sense filtrated sodium. The juxtaglomerular cells, which are also known as the arterial cells, sense a drop in BP and release an enzyme called renin. The release of renin results in the regulation of blood pressure via the renin-angiotensin-aldosterone system, which regulates reabsorption of water and maintenance of intravascular volume. (41, 42)

2.4 HYPERTENSION

More than 95% of hypertensive patients present with essential hypertension, the cause of which is unknown, and the remaining 5% of adults have secondary HT. (43)

Secondary hypertension is commonly understood as HT attributable to a specific and potentially treatable cause. The most common cause is renal artery stenosis. SBP of 120-129 mmHg and DBP of below 80 mmHg (but not less than 60 mmHg) are considered to be normal blood pressure. Abnormal BP is additionally classified as mild, moderate or severe. Mildly raised BP is regarded as SBP of 130-139 mmHg with DBP of 80-89 mmHg, moderately raised BP is SBP of 140-159 mmHg and DBP of 90-99 mmHg, while severe HT is considered to be SBP of more than 160 mmHg and DBP of more than 100 mmHg. (43, 44)

Renovascular HT is elevated BP caused by renal hypotension, usually due to anatomic stenosis of the renal artery resulting in inappropriate activation of the renin angiotensin system. (3, 12, 13, 45)

2.5 RENOVASCULAR HYPERTENSION

2.5.1 Aetiopathogenesis

In patients with RVH, the most common cause of RAS is atherosclerosis, which predominantly occurs in the elderly. It accounts for 90% of the cases of RAS and involves the
proximal third of the main artery, ostium and peri-renal aorta. Atherosclerosis is far more prevalent in men than in women, with a two to one ratio.\(^{(8, 46 \text{ and } 47)}\)

The second most common cause is FMD occurring in women younger than 35 years. It accounts for less than 10% of the cases of RAS and forms part of a collection of vascular diseases affecting the intima, media and adventitia. The causes of RVH in neonates and infants include renal artery thrombosis after umbilical catheterisation and coarctation of the aorta.\(^{(22, 48, 49)}\)

Other causes of RVH include extrinsic renal artery compression by renal cysts or tumours and embolic renal artery occlusion. Neurofibromatosis type 1, which is a rare autosomal dominant disorder, also occurs in children.\(^{(50)}\)

### 2.5.2 Pathophysiology of renal artery stenosis

The changes that occur in RAS are sensed in the Juxtaglomerular (JG) region by an amalgamation of mechanisms: an afferent arteriolar baro-receptor or stretch receptor; a distal tubular sensor of filtrate flow and sodium concentration; and post-ganglionic sympathetic nerves. The renal JG cells are sensitive to pressure changes within the afferent arteriole and, immediately after detecting a fall in blood pressure, they secrete renin. The macula densa in the tubular portion of the JG apparatus are sensitive to sodium chloride moving past them; they are responsible for triggering the secretion of more renin. The granular cells increase neuronal sympathetic activity.\(^{(21, 22, 45, 51, 52)}\)

A stenosis of over 70% is large enough to cause significant hypo perfusion. This results in significant flow reserve in the affected artery.\(^{(46, 52, 53)}\)

RVH depends on secretion of renin from the juxtaglomerular apparatus of the stenotic kidney due to a reduced perfusion pressure distal to the stenosis. Renin converts angiotensinogen, a plasma protein synthesised by the liver, to angiotensin I,\(^{(54)}\) on passing through the lungs via pulmonary circulation, angiotensin I is converted to angiotensin II by ACE, which is an important biologically active molecule that is more abundant in the pulmonary capillaries.\(^{(55)}\) Angiotensin II is the main stimulus for secretion of the hormone aldosterone by the adrenal cortex and thereby has a responsibility, in a similar way as an ischaemic kidney in the constriction of the efferent arteriole, to maintain glomerular filtration rate regardless of reduced perfusion.\(^{(56, 57)}\) Figure 2.1 summarizes the physiology of the renin angiotensin aldosterone system.\(^{(58)}\)
2.5.3 Function of renin angiotensin aldosterone system

Aldosterone increases sodium reabsorption by distal and collecting tubules. The nett result is a greater passive inward flux of sodium into the tubular cells from the lumen and increased active pumping of sodium out of the cells into the plasma. The renin angiotensin aldosterone system thus promotes salt and water reabsorption and a rise in arterial blood pressure. Acting via negative feedback, this system alleviates the factors that triggered the initial release of renin, namely salt depletion, plasma volume reduction and decreased arterial blood pressure. (58, 59)

2.5.4 Manifestations of renovascular disease

RAS may manifest in three, progressive ways: asymptomatic RAS; RVH; and ischaemic nephropathy, stroke and secondary aldosteronism as shown in Figure 2.2. (18)
2.6 CLINICAL AND LABORATORY EVALUATION

The evaluation of patients with RVH is done by taking a proper detailed medical history, conducting a general examination, determining the level of renal function (urea and creatinine levels, electrolyte status, glucose intolerance test, and lipid profile and renal organ damage), taking blood samples for renin levels and non-invasive imaging of the kidneys. (61)

Therefore, it is prudent to rule out other causes of hypertension and perform further meticulous evaluation of the kidneys in terms of clinical history as well as focused laboratory and imaging investigations.

2.6.1 History and examination

Evaluation of the kidneys in patients with suspected RVH includes history and duration of hypertension, age of onset, past medical and family history of the patient, amount of antihypertensive medication that the patient has been taking, the BP trend since the initiation of therapy, as well as a thorough clinical evaluation of all systems, including the abdomen (for abdominal bruit). Furthermore, elucidation of clinical signs of renal failure like lower limb oedema, puffy eyes, polydipsia, tiredness and flank pain which may indicate worsening of renal function is important in a patient with suspected RVH. (62, 63)

2.6.2 Patient workup

Numerous diagnostic tests have been proposed to detect RVH and an ideal screening test has not been established because an acceptable test for RVH should be able to demonstrate the
presence or absence of RAS, be able to localise it, assess its haemodynamic significance, and predict cure and better outcome. \cite{64,65} In addition, the ideal test must be safe, simple and inexpensive with high sensitivity and specificity. Such an ideal test for RVH does not exist. \cite{67} Therefore, the goals of screening tests are to detect RAS-induced HT amenable to surgical cure. \cite{67,68}

2.6.3 Metabolic profile and other markers

2.6.3.1 Renin sampling

The relationship between RAS and a patient’s systemic hypertension has been tested by renin sampling of the renal vein. The test is considered positive when renin is 1.5 times higher than normal. A positive test means that the stenosis is sufficient to produce HT. Normal renin levels are 0.2-1.6 ng/ml/hr. The differences associated with preparation of the patient, technical expertise and handling of sample result in widely incongruent results. Many false positive results have been recorded, which are merely because the HPT becomes sustained and there is reduction in plasma renin activity, denoted as reverse tachyphylaxis. \cite{46,69} It is an invasive, time-consuming and costly technique. Studies have shown that there is a need to discontinue medications that may interfere with the studies, which further compromises the wellbeing of the patients.

Renal vein renin levels obtained after withholding ACEI therapy for the duration of two weeks indicate that values of 1.5 times higher, more accurately predict the fall in arterial pressure following nephrectomy in patients with complete occlusion, but in practice, clinicians are not willing to withdraw drugs for that long, resulting in less consistent results. \cite{70,71}

Renal vein sampling has a sensitivity of 69% and specificity of 29% in the detection of RAS. The drawback in specificity is its inability to differentiate the affected from the non-affected kidney and the notion that plasma renin levels may be elevated in normal patients lying in a recumbent position. \cite{72}

2.7 RENAL SCINTIGRAPHY

2.7.1 Normal kidneys on scintigraphy

In order to understand the appearance of the kidneys and abnormalities associated with them, it is important to have knowledge of how they appear on this imaging modality. \cite{21,73}
Renal dynamic functional studies are generally acquired in two parts. Renal blood flow is assessed in the first pass of the radiopharmaceutical bolus in the kidneys; the arrival in the kidneys is represented by the vascular transit which lasts for 30-60 seconds. The second phase is called the cortical concentration phase, which occurs between 1 and 5 minutes and corresponds to a rising part of renal time/activity curve. The relative function of a kidney is calculated during this uptake phase. The clearance or excretion phase is a result of radiopharmaceuticals being cleared from the kidney and collecting system.\(^{22,74}\)

Interpretation of a renogram is composed of flow and cortical function phases. Blood flow to the kidneys is normally seen within 2 to 5 seconds of abdominal aorta visualisation; this is described as prompt perfusion, corresponding to the passing of bolus of tracer within the blood vessels immediately after the administration of a radiopharmaceutical. Any asymmetry in tracer activity suggests abnormal perfusion. Normally, the kidneys curves should peak by 1 to 5 minutes and ideally contain equal activity. Half of the peak activity should be cleared from the kidneys by approximately 8 to 12 minutes.\(^{75,76,77}\)

Normal kidneys should also be able to accumulate tracer in the parenchymal tissue within the first 1 to 3 minutes. The radiopharmaceutical clears into the bladder by the end of the study with normal visualisation of the bladder and overall the process lasts for 25-30 minutes.\(^{21,78}\)

Renal function is measured by the ability of the kidneys to clear certain substances from the plasma. The preferred RP is Tc-99m DPTA (diethylene triamine pentaacetic acid) which is excreted by the glomerulus and ACEI acts mainly by decreasing the intra-glomerular hydrostatic perfusion pressure. The RP for assessing renal function are grouped into three categories namely: those excreted by glomerular filtration like Tc-99m DTPA, those excreted via tubular secretion like Tc-99m MAG3 (mercaptoacetyl triglycine) and those retained in the renal tubules like Tc-99m DMSA (dimercaptosuccinic acid).\(^{79}\)

Tc-99m MAG3 is protein-bound and cleared predominately by proximal tubules with minimal glomerular filtration. As a tubular agent, it has superior renal extraction when compared to Tc-99m DTPA and provides better quality images, making it the agent of choice, especially in children and patients who have compromised renal function.\(^{80}\)
Figure 2.3 Normal renal scintigraphy - Both kidneys are promptly perfused and demonstrate fairly uniform concentration with normal excretion, this is quantified with the renal washout curves. The numbers indicate minutes post injection.\(^{(60)}\)

2.7.2 Imaging workup: Functional or radionuclide imaging

2.7.2.1 The rationale for using angiotensin converting enzyme inhibitor

The development of ACEIs has improved the diagnosis of RVH and the single-dose captopril is considered to be the best screening test for identification of RVH. A significant renal stenosis (60-70%) decreases arteriolar blood pressure, which stimulates renin secretion by the juxtaglomerular apparatus.\(^{(81)}\)

Captopril, which is an ACEI, acts to block the conversion of angiotensin I to angiotensin II, which induces efferent arteriole vasodilatation, thus post-capillary resistance is decreased and the filtration pressure and GFR falls if the kidney has significant RAS.\(^{(19)}\)

Captopril renography is a functional and non-invasive diagnostic test for renin-dependent RVH. It is useful in the detection of either unilateral or bilateral reduction of renal function or the detection of dependence of angiotensin II GFR.\(^{(86)}\)
Captopril-enhanced renal scintigraphy has been shown to be sensitive in detecting those patients who would benefit from revascularisation or angioplasty and those who might benefit from captopril therapy in order to preserve renal function and further eliminate possible life-threatening complications.\(^{(12, 82)}\)

Functional captopril-augmented imaging is performed using a number of radiopharmaceuticals, including Tc-99m DTPA and Tc-99m MAG3. Iodine-131 orthiodohippurate (I-131 OIH) may also be used, but not practical due to non-availability and higher cost.\(^{(83)}\)

In a one day protocol the ACEI and baseline renography are done on the same day. A two day protocol is done over two different days. In a two day protocol, the ACEI renography should be performed on the first day. If ACEI renography is normal, the possibility that the patient is having RVH is low and there is no need for the patient to come for a baseline renography. Baseline renography which is performed in the absence of an ACEI is done to maximize the specificity of the test\(^{(19, 84)}\).

2.7.2.2 Tc-99m diethylene triamine pentaacetic acid

The main role of Tc-99m DTPA is to ascertain differential renal function and excretion; this is because glomerular function is decreased when there is low hydrostatic pressure in the glomerulus which is also used to detect hypo perfusion.\(^{(84)}\) Tc-99m DTPA is a heavy metal chelator which is cleared through glomerular filtration.\(^{(85)}\) It is the most widely used and preferred radiopharmaceutical for imaging patients with suspected RVH. The advantages of Tc-99m DTPA are that it is mainly excreted by glomerular filtration, less expensive and simpler to radiolabel. Its limitations include a poor target-to-background ratio.\(^{(12, 13, 85)}\)

Following IV injection, the first thing that is seen is the perfusion or vascular transit phase, then a progressive rise: the curve starts to go down when excretion (into the calyces and ureters) is superior to concentration/accumulation in the tubes. Peak cortical uptake occurs within 3 to 4 minutes, the collecting system by 5 minutes and the bladder is typically visualised by 10-15 minutes.\(^{(12, 13, 86)}\) The dynamic renal images and transit curves display the initial transit of arterial blood containing the radiopharmaceutical.\(^{(21, 87)}\)
The criteria for interpreting RVH on a Tc-99m DTPA

In a Tc-99m DTPA study, the tracer uptake is exclusively filtered by glomeruli, reflecting split GFR. A greater than 10% reduction in differential function post-ACEI indicates a high probability of RVH. Values between 5 and 9% indicate an intermediate probability of RVH and marked unilateral decrease in differential function after ACEI when compared to the baseline study may be compatible with high probability of RVH.\(^3, 28, 35, 88\)

2.7.2.3 Tc-99m mercaptoacetyl triglycine

Tc-99m-MAG3 is cleared almost exclusively by tubular secretion, which results in better quality images. The better quality images are due to the fact that the clearance is higher than that of Tc-99m DTPA. The background activity decreases faster and results in better contrast. The radiopharmaceutical has a much higher extraction fraction.\(^12, 13, 14\) The normal time for Tc-99m MAG3 is almost the same as for Tc-99m DTPA because it is related to minimum tubular transit time.\(^89\)

The criteria for interpreting RVH on a Tc-99m MAG3 scan are as follows:

a. Unilateral retention of tracer within the parenchyma is the most important criterion for Tc-99m MAG3 in the diagnosis of RVH, representing a probability of more than 90% for RVH. This can be measured by a prolonged transit time, a change in 20 minutes/peak ratio of 0.15 or greater or a change in renogram.

b. When there is a decrease in unilateral uptake of more than 10% on the ACEI study when compared to the baseline renography. A decrease of between 5 and 9% is considered to indicate an intermediate probability of RVH.\(^3, 90\)

c. In cases of severe stenosis (over 95% occlusion), a rising baseline renogram with no further deterioration after ACE inhibition may be seen. Because of the severity of the occlusion, the RAS compensation is no longer adequate to maintain renal perfusion. This is not a specific finding however as the same pattern may also be visualised in other conditions such as acute tubular necrosis, drug toxicity, interstitial or glomerular nephropathies, complete obstruction, and renal vein thrombosis.\(^90\)

d. Non-visualisation of the kidney may be as a result of renal artery obstruction, indicating a kidney that may be surviving on collaterals and does not function, which may induce RVH.\(^10, 12, 33, 91\).
In general, accuracy of the ACEI-augmented scintigraphy is optimal in the absence of renal insufficiency; it reflects true RVH and not simply the presence of RAS (since RAS does not necessarily cause hypertension).

Grading of time-activity-curves (TAC) qualitatively and semi quantitatively on temporal parameters is reflected in Table 2.1 below \(^{(12, 33, 90)}\):

<table>
<thead>
<tr>
<th>Grading</th>
<th>Analysis</th>
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<tbody>
<tr>
<td>Grade 0</td>
<td>Normal accumulation gradient  (T_{max} = 3-5) minutes  *  Normal urinary excretion</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Mild delay in upslope  (6) minutes (&lt; T_{max} \leq 11) minutes  *  Normal urinary excretion</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>Considerably more delay in the upslope  (T_{max} &gt; 11) minutes  *  Evident urinary excretion</td>
</tr>
<tr>
<td>Grade 2B</td>
<td>Considerably more delay in upslope than Grade 1  (T_{max} &gt; 11) minutes  *  No evidence of an excretory phase</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Marked reduction or absence of uptake</td>
</tr>
</tbody>
</table>

Table 2.1: Grading of TAC renographs

Grading-based outcome of scintigraphic ACEI-augmented analysis \(^{(90, 91)}\):

\(\text{a. High probability for hemodynamically significant RAS:}\) this is reflected by a change in grade between baseline and post-ACEI studies which indicates significant reduction of renal function after ACEI augmentation compared to the baseline study; a high probability (Table 2.2) carries a high predictive value (90\%) that RAS is present and that there will be reduction or cure in hypertension post-revascularisation; further contrast angiography diagnostic work-up performed on this group would not be considered cost-effective:

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Post-Captopril</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 0 or 1</td>
<td>Grades 2A, 2B, or 3</td>
<td>High</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>Grades 2B or 3</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 2.2: Probabilistic interpretation of changing grades

\(\text{b. Intermediate probability for haemodynamically significant RAS:}\) this is characterized by persistent unchanged abnormality in renograms of ACEI-augmented and baseline studies, i.e., a baseline Grade 2B or Grade 3 which does not become worse
post-ACEI; the majority of patients belonging to this group have hypertension with ischemic nephropathy characterized by azotemia and/or small kidneys with poor function – the absence of renin-dependent hypertension most likely accounts for the false-negative results in this population. This group of patients may be referred directly for contrast angiography because poor renal function may most likely result in a non-diagnostic scintigraphic examination; however, they may also benefit from revascularisation procedures in an attempt to improve renal function and ameliorate co-existing hypertension.

c. Low probability for hemodynamically significant RAS: normal Grade 0 groups with normal ACEI renogram; hypertension is unlikely to improve with revascularization in this group of patients compared to those with positive test results because of the absence of significant renal artery lesion; further diagnostic tests for RVH are therefore not indicated.

Apart from the use of captopril in the diagnosis of RVH, enalapril at a dose of 0.04mg/kg per intravenous route has been tested with success. Conversely, non-steroidal anti-inflammatory drugs such as aspirin or angiotensin receptor blockers (e.g. valsartan) have not given better results than captopril. The rationale of doing aspirin renography is that prostaglandin E2 is higher in a stenosed kidney and the increased levels assist in maintaining blood flow. Aspirin renography inhibits prostaglandin synthesis in order to detect unilateral renal stenosis. Even though the mechanism of ACEI differs from that of non-steroidal anti-inflammatory drugs, their combination may further improve the negative predictive value of the test to exclude RVH. (12, 92)

2.7.3 Ultrasonography

Ultrasonography (U/S) is an essential tool that can be used to measure the size of the kidneys because it better denotes anatomical details of the kidneys. The mean renal length of the right and left kidney is 10.68 cm ± 1.4 cm and 10.71 cm ± 1 cm respectively. The actual kidney is directly correlated with the height, age and body mass of the patient. When the kidneys are well matured and fully developed, they resemble the size of a fist. (93, 94, and 95)

Doppler U/S has been found to be paramount in the measurement of blood velocity. The technique is non-invasive, simple, affordable, done at the patient’s bedside and highly
sensitive when used by an expert. It can also be used in the detection of RAS. High rate of technical failure and lack of reliability are some of the draw backs of renal U/S. (95, 96)

A sonographic index known as resistance index (RI) is used to evaluate renal arterial disease; it subtracts the end diastolic velocity from the peak systolic velocity over the peak systolic velocity. The normal value is between 60-70%. An elevated RI suggests structural abnormalities in small vessels of the kidney and benefit from renal revascularisation has been reported in patients with RI of 80%. (97)

Duplex U/S can offer images of renal arteries and also gives information on blood flow velocity and pressure waveforms; however, there is a 10-20% rate of failure due to lack of operator experience or the presence of obesity. (98)

The sensitivity of U/S in the detection of RAS is within the 60% range with more than 20% technically inadequate studies, often due to obesity or poor preparation. Duplex U/S has fewer false positives but that does not mean it cannot miss important vascular lesions. (100)

2.7.4 Magnetic resonance imaging

Gadolinium-enhanced angiography provides detailed information on the size of the kidney and accurate morphology of renal arteries. A more detailed examination consists of 3D dynamic gadolinium-enhanced and a 3D phase-contrast magnetic resonance angiography (MRA) technique which permits imaging of visceral organs and renal arteries. 3D gadolinium-enhanced MRA has shown to generate tremendous contrast enhanced angiograms devoid of risk of further exposing patients to ionising and avoidable radiation. It has a noticeable advantage over conventional angiography in the convenience of determining the clinical importance of suspicious lesions. (101, 102)

The 3D phase contrast method is flow centred and provides functional and high-resolution images that jointly compute renal perfusion. There are, however, patients who were reported to have shown poor contrast enhancement. MRA is only limited to blood flow within the renal arteries and further assessment of the perfusion within the kidney itself may necessitate an MRI with arterial spin. Gadolinium contrast has a drawback of having a low signal-to-noise ratio and reduction in spatial resolution. MRA is also not widely available, is costly and has a lengthy imaging time, which may be a concern in claustrophobic patients and may also pose difficulty in grading renal vessel stenosis. (103, 104)
MRI is therefore useful in providing anatomic information about vascular stenosis, but it has limitations in providing the functional consequence of that stenosis.\(^{(105)}\)

While gadolinium contrast is considered safe for patients with preserved GFR, a newer technique allows improved vascular imaging without gadolinium contrast. The sensitivity and specificity of 3D phase-contrast MRA in the detection of RAS is more than 90%, especially when the stenosis is located in the proximal third of the renal arteries. In this instance found to have an accuracy of 98%.\(^{(106, 107)}\)

### 2.7.5 Computed tomography angiography (CTA)

Angiography uses the intravenous administration of contrast media to depict arterial circulation, which further detects both the lumen and vessel wall, but with limited resolution for distal parts of the renal vessels.\(^{(108)}\)

CTA is an accurate and non-invasive quantitative method in the diagnosis of RAS. The quality of continuous data obtained from a region of interest during a single breath-hold gives sufficient information to reconstruct 3D images. Although it is an invasive procedure, it is still the gold standard for detection of renal artery stenosis caused by FMD. CTA can also display secondary signs of RAS; it also demonstrates renal vascular anatomy, parenchymal changes, infarcts and atrophy.\(^{(109,110)}\)

Harrington\(^{(110)}\) states that “digital subtraction angiography (DSA) is a computerized radiographic method that uses intravenous bolus injections of standard contrast material (IV DSA) or as an adjunct to intra-arterial digital subtraction angiography (IA DSA)”. Intra-arterial digital angiography has largely replaced IV DSA since it requires a lesser amount of radio contrast of 25-50 ml as compared to conventional angiography in evaluation of patients for RVH. IA DSA is therefore ideal for patients with dysfunctional kidneys. Conventional angiography requires 100 ml of contrast.\(^{(110,111)}\)

CTA has the advantage of being able to be performed on an outpatient basis. It is a widely available procedure, particularly in developing countries. CTA should be performed in patients with normal or near-normal renal function. Intravenous contrast medium can cause contrast-induced nephropathy in patients with chronic kidney disease. The nephropathy occurs when serum creatinine increases by more than 25% within three days after injection of an IV contrast in the absence of an alternative diagnosis.\(^{(112)}\)
2.8 MANAGEMENT OF RENOVASCULAR HYPERTENSION

Medical management

- Anti-hypertensive drug therapy.
  - ACE inhibitors.
  - Angiotensin receptor blockers.
  - Calcium channel blockers.
  - Beta blockers.
- Diuretics.
- Vasodilators.
- Lipid reducing agents.

Cardiovascular risk factor reduction

- Stop smoking.

Renal revascularization

- Endovascular procedure.
- Percutaneous trans renal angiography (PTRA) with stenting.

Surgical procedures

- Renal artery reconstruction.
- Renal endarterectomy.
- Resection and anastomoses.

External anatomic procedures

- Spleno-renal bypass.
- Hepato-renal bypass.
- Laparoscopic or direct nephrectomy.
CHAPTER 3
MATERIALS AND METHOD

3.1 INTRODUCTION

Nuclear medicine renography is a well-established practice which includes ACEI-augmented renography, dynamic and renal cortical scintigraphy studies and glomerular filtration rate determinations.

This chapter serves to demonstrate data and theoretical analysis of methods applied to this study. It includes the study design, research settings, study population, sample size, data collection methods and analysis, ethical considerations, and validity and reliability of the research methods.

3.2 THE STUDY DESIGN

The study was a hospital-based retrospective audit evaluating the compliance and adherence to the referral system for ACEI-augmented renal scintigraphy in patients with suspected RVH.

Patient files were reviewed in order to ascertain which patients were rightfully referred for ACEI-augmented renal scintigraphy. The study population entailed archives of patients obtained from storage in the department of Nuclear Medicine at DGMAH.

Data were collected from studies that spanned over a period of seven years between June 2009 and June 2016. The data were collated, checked for quality, entered and analysed, and a final manuscript was written.

The EANM guidelines were adapted and collated into a data collection instrument in the form of checklist of the criteria, which was applied to the study.

3.3 THE STUDY POPULATION

The study was conducted in the department of Nuclear Medicine DGMAH, in Ga-Rankuwa, Gauteng province.

The study comprised patient files which were retrieved from archives of patients with suspected RVH who were referred to the department of Nuclear Medicine DGMAH. All patients met the criteria for inclusion as mentioned below:
Inclusion criteria:

- All request forms or records for ACEI renal studies performed on children and adults.

Exclusion criteria:

- All studies referred to the department of Nuclear Medicine at DGMAH for ACEI renography with poor renal function.
- Files/records with incomplete/missing pertinent information, viz:
  - Blood pressure readings not recorded.
  - Age of the patient not stated.
  - Specific radiopharmaceutical utilized not recorded.

3.4 SAMPLING AND SAMPLE SIZE

It was anticipated that, over the retrospective data collection period, approximately 140 patient files in which ACEI renal studies done would be recruited. A sample size of 140 was estimated at a 90% confidence interval with an expected frequency of 50%. This estimation was performed on Epi Info™ 7.

3.5 METHODS OF DATA COLLECTION

The files of all included patients with clinically suspected RVH and who underwent ACE inhibitor augmented renal scintigraphy were retrieved. Demographic data, including the patient’s age and gender, were recorded. The following parameters were recorded: SBP and DBP, severity and nature (refractory) of hypertension, patient’s age, the presence or absence of an abdominal bruit, grade 3 or 4 retinopathy, recurrent pulmonary edema, unexplained azotaemia, worsening of renal function and umbilical catheterisation in children. If no clear criteria were obtained from the records, “unspecified indication” was recorded on the data collection sheet.

3.5.1 RVH imaging protocol

In all patients, dynamic radionuclide renography was performed following the intravenous injection of a RP specific for the kidneys. Images were acquired with a gamma camera (Ecam; Siemens Mechanical Solution USA, Inc.) equipped with low-energy, parallel-hole, high-resolution collimators. The patients were imaged lying supine with the detector positioned posteriorly. Dynamic acquisition was acquired in two parts, the first phase being assessment
of blood flow immediately after the patient was injected with a bolus and imaged at 1-2 sec per frame for 60 seconds. The second part of imaging was acquired at 30 seconds per frame for 25-30 minutes. Pre and post void imaging were also acquired for all patients.

3.5.1.1 Imaging protocol

Two studies were performed, one with an ACEI augmentation and one without. All patients were thoroughly prepared before each study.

Patient preparation included the following for both components of the study:

- The patients were well hydrated. They were advised to drink about 500 ml water over an hour at least 48 hours prior to the study, or they were hydrated through intravenous (intravenous (I.V) infusion (10 ml/kg), which is more applicable for inpatients in order to limit false positive results as a result of stasis of tracer within the kidneys.
- The patients fasted for at least eight hours in order to allow maximum absorption of oral captopril.
- The IV line was kept in situ until the end of the study to correct ACE-related hypotension.
- ACEIs were discontinued as follows:
  - Short-acting drugs like captopril for a duration of 48 hours.
  - Long-acting ACEI like Lisinopril and enalapril for a week before examination.
  - Other medications like calcium channel blockers and diuretics that could affect the sensitivity of the study were also discontinued.
- Captopril (25-50 mg) was crushed and dissolved in water and swallowed per mouth one hour before injection of tracer.
- Blood pressure measurements were taken every 15 minutes post ACEI administration and the patients were carefully monitored for hypotension until the end of the imaging. The patients were then discharged after retaining their baseline blood pressure.

The study procedure was as follows:

- A two-day protocol was performed – ACEI augmented and baseline renal scintigraphy was performed a week apart. The same radiopharmaceutical (either Tc-99m MAG3 or Tc-99m DTPA) was used for both studies in the same patient for the two components of the study.
• Lasix was administered 20 minutes after the radiopharmaceutical to ensure clearance of the collecting system to avoid false positive results.

3.5.1.2 Image interpretation

The ACEI causes a drop on the side of stenotic artery which subsequently leads to a decrease in urine production, which manifests in the functional portion of the study as abnormally reduced function when compared to the baseline study. The diagnostic pattern depends on the radiopharmaceutical used.

The criteria used in the evaluation of RVH using the tubular agents Tc-99m MAG3:

• Prolonged cortical retention which occurs as a result of reduced urine flow, which causes diminished washout of radiotracer into the collecting system. It quantitatively appears as an increase in cortical retention.
• The mean parenchymal transfer time increases to over 240 seconds, or just above the baseline.
• The cortico-pelvic transfer time (time interval between first appearance of kidney activity and the first appearance of pelvic activity) increases.
• Split renal function may decrease. The change in renal function is not commonly appreciated in MAG3 but, if it does occur, it is considered to be significant.
• An increase of time to peak activity of more than five minutes after administration of captopril as compared to baseline is considered to be suspicious and should be interpreted hand-in-hand with other parameters.
• Non-visualisation of the kidney, which is usually seen in patients with complete renal artery obstruction without major collaterals, will be apparent in both baseline and ACEI studies.
• The presence of a rising baseline renogram is seen in instances of severe stenosis of more than 95%. In these patients, renin-angiotensin compensation is no longer adequate to maintain renal perfusion since there will be no change.

The criteria used in evaluation of RVH in Tc-99m DTPA ACEI are as follows:

• A reduction in cortical uptake lasting two to three minutes is expected to occur.
• A unilateral reduction in differential function of at least 5-9% or greater than 10%. (21, 90)
• Marked unilateral retention of tracer may represent high probability for captopril study.
3.5.1.3 Reporting

A normal study denotes low probability for renin-dependent RVH, meaning that the probability of RVH after the test is 10% or less.

An intermediate probability of RVH as a consequence of RAS is reported in patients with abnormal baseline scan with no change in the ACEI study, for example in patients with unilateral small kidney and bilateral cortical retention. It may also be interpreted as no change in renogram curve/grade.

High probability denotes that the chances of RVH in this patient are greater 90% and the patient would improve on angioplasty or surgery. Deterioration of renogram grade following captopril administration is deemed to indicate high probability of RAS.

Bilateral cortical retention may be due to bilateral renal artery stenosis in 5-15% of the cases and the majority are as a result of dehydration, hypotension and the failure to stop calcium channel blockers prior to the study.

When the study protocol has been properly adhered to, sensitivity and specificity of ACEI renal scintigraphy have been reported to be approximately 90-95% respectively.

3.6 ETHICAL CONSIDERATIONS

In a retrospective study which involves data collection from archived records, there is no need to obtain patient consent.

Approval of the study was obtained before commencing the study in the form of a clearance certificate from School Of Medicine Research Ethics Committee and Sefako Makgatho University Research Ethics Committee.

There was no mention of the patients’ names in the data collection sheet. Furthermore, information gathered from the study has been treated with high degree of confidentiality.

Permission to conduct the research was sought from the clinical management of DGMAH and the head of the department of Nuclear Medicine.

3.6.1 Approval of the study
The research protocol was approved by Sefako Makgatho University Research and Ethics Committee. Approval to conduct the study was also obtained from the hospital clinical manager of the DGMAH.

The certificate of approval is attached as appendix 3.

3.7 MEASURES TO MINIMISE BIAS, ENSURE RELIABILITY AND MAINTAIN CONSISTENCY

The following measures were taken to ensure that the records were represented as they were:

- The data extracted from the patient records were reviewed by two independent and blinded observers (qualified nuclear physicians).
- The data collection tools that were used were drawn up in consultation with experienced Nuclear Medicine consultants.
- The patient files were readily available in the records room.
- The data in the request form were cross-checked against the medical records contained in the individual patient files. Since these medical records are considered to be legal documents, the data contained therein were presumed truthful and reliable.
- To minimise bias, the independent observers had not seen the previous results of the patients.

3.8 HAZARDS TO THE PATIENT AND OTHER ETHICAL ISSUES

This study did not pose any risk to the patients because it is a retrospective study in which only patients’ records were evaluate.
### 3.9 RESEARCH TIMELINE

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CHAPTER 4

RESULTS

4.1 INTRODUCTION

In this chapter, the results and interpretation of findings are presented. The chapter is presented in the following manner: demographic information of the patients; BP in terms of SBP and DBP; the rest of the parameters, which include gender, age, manner of onset of HT, severity of the HT, unexplained azotaemia, abdominal bruit, uncontrolled HT, refractory HT, grade 3 and 4 retinopathy, age of onset, pulmonary oedema, umbilical catheterisation and those with unspecified indication; the outcome of the scans; and the radiopharmaceuticals and their outcome.

4.2 PATIENTS’ DEMOGRAPHIC INFORMATION

A total of 140 patients (71 females and 69 males) with suspected RVH who had undergone captopril augmented scintigraphy were included in the study. The ages ranged between 3 and 82 years (mean age 30.19 years). The majority of the patients (65%) were below the age of 30 years (Table 4.1).

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>92</td>
<td>65.7%</td>
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<tr>
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<td>&gt;55</td>
<td>08</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

Table 4.1 Age distribution of the patients

4.3 SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

The BP was classified according to normal values for children and for adults. Blood pressure is considered to be normal when the SBP is not more than 120 mmHg and the DBP is not more than 80 mmHg. In children, normal blood pressure is defined as SBP of not more than 106 mmHg with DBP of not more than 63 mmHg.

Overall, out of a total of 140 patient files evaluated 22 (15.7%) had normal SBP and 45 of the patients (32.1%) had normal DBP. All patients who had normal SBP also had normal DBP, but not all patients with normal DBP presented with normal SBP. Out of 45 patients with normal DBP (32.1), 29 had abnormal SBP (20.7). 31 (22.1%) of the patients had mildly elevated SBP and 33 (23.6%) had mildly elevated DBP. 45 patients (32.1%) had moderately
increased SBP and 34 (24.3%) had moderately increased DBP. The second highest number was seen in the group of 42 patients (30%) who had severely elevated SBP and 28 (20%) who had severely elevated DBP. This is presented in Figure 4.1.

![Diastolic and systolic blood pressure](image)

**Figure 4.1** Systolic and diastolic blood pressure measurements of all patients (irrespective of scan result).

### 4.4 ANALYSIS OF COMPLIANCE OF RETROSPECTIVE DATA USING EANM GUIDELINES (N=140)

Among the guidelines of the EANM, the most frequent indication (58/140=41%) for renography was an onset before the age of 30. The second most frequent indication (23/140=16.4%) was uncontrolled HT. The third most frequent indication was severe HT (8/140=5.7%). The fourth most frequent indication was refractory HT (5/140=3.6%). The fifth was abdominal bruit (3/140=2.1%) and only 1 patient out of the 3 had a positive renography. The sixth was retinopathy (1/140=0.7%) and the patient had a positive renography.

It is, however, remarkable that a large fraction of the sample (48/140=30.1%) were referred with no clearly defined indications/criteria for renography according to the EANM guidelines. Out of the 48 patients with unspecified indications, 2 had positive renography.

These indications are shown in Table 4.2.
### Table 4.2 Analysis of compliance to the guidelines

** The summed total is 146, which is greater than the number of patients (140) because some patients had multiple EANM guideline criteria (e.g. Age<30 and severe hypertension and abrupt onset etc.)

** 4.5 POSITIVE AND NEGATIVE RESULTS

#### 4.5.1 Positive studies

Out of 140 patients, 10 (7.1%) had positive ACEI renal scintigraphy. The remaining 130 (92.9%) had negative studies.

Among the patients presenting with positive scans:

- Age: five (50%) were younger than 30 years and five (50%) were older than 30 years.
- SBP: eight (80%) had abnormal SBP and two (20%) had normal SBP.
- DBP: Six (60%) had abnormal DBP and four (40%) had normal DBP.

“As a reminder, a normal BP corresponds to SBP between 120 and 129 mmHg and a DBP between 60 and 80 mmHg. A mild corresponds to SBP between 130 and 139 mmHg and a DBP of 80-89 mmHg. A moderate HT corresponds to a SBP between 140 and 159 mmHg and a DBP between 90 and 99 mmHg. A severe HT corresponds to a SBP above 160 mmHg and a DBP above 100.”(43, 44)
Among the ten patients presenting with positive renography, two (20%) had normal BP, one (10%) had mild HT, one (10%) had moderate hypertension and six (60%) had severe HT (Figure 4.2).

![Blood pressure measurements in positive studies](image)

**Figure 4.2 Blood pressure measurements in positive studies**

### 4.5.2 Negative results

130 of the 140 patients (92.9%) had a negative ACEI study. 88 (67.7%) were below the age of 30 years and 42 (32.3%) were older than 30 years.

With respect to BP measurements in this group:

- 22 (16.9%) had normal SBP
- 43 (33.1%) had normal DBP
- 26 (20%) had mildly elevated SBP
- 30 (23,1%) had mildly elevated DBP
- 47 (36.2%) had moderately elevated SBP
- 32 (24.6%) had moderately elevated DBP
- 35 (26.9%) had severely elevated SBP
- 25 (19.2%) had severely elevated DBP
4.6 RADIOPHARMACEUTICALS

The highest number of patients (98/140=70%) were imaged using Tc-99m DTPA and 42 patients (30%) were scanned using Tc-99m MAG3.

The positive studies are summarised in table 4.3 below:

<table>
<thead>
<tr>
<th>Criteria used – Tc-99m DTPA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral reduction in differential function</td>
<td>7</td>
</tr>
<tr>
<td>Reduction in cortical uptake of 2-3 minutes</td>
<td>0</td>
</tr>
<tr>
<td>Unilateral retention of tracer</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria used – Tc-99m MAG 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged cortical retention</td>
<td>2</td>
</tr>
<tr>
<td>Change in renal function</td>
<td>0</td>
</tr>
<tr>
<td>Non visualisation of the kidney</td>
<td>0</td>
</tr>
<tr>
<td>Rising baseline renogram</td>
<td>0</td>
</tr>
<tr>
<td>Increase in cortico-pelvic transfer time</td>
<td>0</td>
</tr>
<tr>
<td>Increase in time to peak</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4.3 Positive studies as per criteria for each respective radiopharmaceutical
4.7. Statistical analysis

In accordance with the second objective (see section 1.4), the rate of adherence to the guideline was calculated. An analysis was made of the outcomes of the ACEI renography in relation to adherence to the guidelines, which was then clinically interpreted. A statistical significance of P<0.05 was used for all the statistical procedures.

Statistical analysis of data was performed using IBM SPSS 24 program running on Microsoft Windows from a personal computer.

Interpretation of the statistically analysed data was used to determine whether or not there was compliance to referral criteria for ACEI-augmented renal scintigraphy in patients with suspected RVH. P values were determined by Chi-square tests.

In my series of patients, severe hypertension was found to be a predictor of a positive scan. A statistical significant correlation was found between the severity of blood pressure and positive scans, (P value of 0.043).

There was similarly statistical significant correlation between the age and elevated diastolic blood pressure, (P value 0.038). This was however expected because of the age related incidence of elevated diastolic pressure with increase in age.

No statistical significant associations were found between the patients referred with an abdominal bruit, worsening in renal function, uncontrolled hypertension, grade 2 and 3 retinopathy, refractory hypertension and the age of the patient in comparison to the number of positive and negative scans (P values all >0.05).
CHAPTER 5

DISCUSSION

This chapter discusses the research results in relation to the existing literature. The chapter is presented in the following order: introduction, patients’ demographic information, correlation with the blood pressure, diagnostic parameters and radiopharmaceuticals. A summary of the important findings, conclusion and recommendations are also included here.

5.1 INTRODUCTION

It is prudent to categorise RVH in terms of moderate and high risk and also to be able to distinguish between RVH and RAS. The ultimate goal of screening these patients is to be able to detect whether the hypertension is as a consequence of RAS and to predict curability of the patients after revascularisation. (3, 19)

In the current study, a remarkably large fraction of the hypertensive population presented with no indication of RVH according to the EANM guidelines. These results are not in keeping with results in other previously conducted studies. (3) Studies have shown that the test can be more cost effective if it is conducted only in patients whose clinical features are associated with moderate to high risk of RVH. These clinical features include abrupt onset, severe hypertension, and refractory hypertension, onset of hypertension before the age of 30 years, worsening in renal failure, abdominal bruit, grade 3 and 4 retinopathy, and onset of hypertension after the age of 50 years. (3, 19)

5.2 PATIENTS’ DEMOGRAPHIC INFORMATION

A total of 140 patients (71 females and 69 males) with suspected RVH who had undergone captopril scintigraphy were included in the study. The ages ranged between 3 years and 82 years, with a mean age of 30.19 years.

Among the 10 (7.1%) patients who had positive renography, five (50%) were below the age of 30 years and an equal number (5/10=50%) were above the age of 30 years, demonstrating no clear difference in patients younger than 30 or above 30 years. This finding is not in keeping with the clinical criteria or guidelines which state that the majority of RVH patients will be below the age of 30 years. (3, 19) It should however be stated that the 5 positive patients above 30 years represents a small group, therefore a clear correlation cannot be established.
There may be a need for a prospective study to determine what percentage of the population group have RVH and are above the age of 30 years.

Even though age <30 was the most consistently followed criterion in this study, it may necessarily not be most important criterion in the population

5.3 THE LEVEL OF HYPERTENSION

Angiotensin II results in elevation of blood pressure following the stimulation of renin by constricting the peripheral vessels, and stimulation of aldosterone and sodium and water reabsorption which is commonly seen in patients with RVH. (7) There are, however, other causes of pseudo-resistant hypertension which may mimic RVH. (4) It is therefore important to exclude other causes of hypertension before investigating patients for RVH using captopril renography.

This study has demonstrated that, among the 140 patients referred for RVH, 22 (15.7%) had normal SBP and 45 (32.1%) had normal DBP. These results are contrary to the studies that showed that, in order to have reproducible results, ACEI renography studies must be done in patients with moderate to high risk for RVH. The above further demonstrates lack of adherence to the guidelines.

Severe hypertension, which is defined as SBP of more than 160 mmHg and DBP of more than 100 mmHg was recorded in 6 (60%) patients with positive renography and this seems to be a reliable criterion in assessing patients for an ACEI renography test.

5.4 REFERRAL CRITERIA IN ACCORDANCE TO THE GUIDELINES

5.4.1 Onset of elevated blood pressure below the age of 30

The majority of the patients (58/140=41.4%) had elevated BP which began before the age of 30 years, but among the 10 patients with positive renography, five (50%) patients were below the age of 30 and five (50%) were above the age of 30 years. This current study has therefore highlighted that age group may not be a true determinant for a positive captopril study.

5.4.2 Uncontrolled hypertension

The second commonest reason for referral in accordance to the EANM criteria was uncontrolled hypertension. It was shown in this study that, despite a relatively high number of
patients (23/140=16.4%) referred due to uncontrolled hypertension, none of these patients yielded any positive results.

5.4.3 Severe hypertension

Out of the total number of 140 patients, 8 (5.7%) had severe hypertension listed as a criterion/indication for the ACEI study on the request form. Among these 8 patients, 2 (25%) had positive ACEI renal scans.

Overall (independent of severity of hypertension listed on the request form), 6 (60%) out of the 10 patients with positive scans met the criteria for severe hypertension.

This indicates that severe hypertension is an important risk factor for RVH in this series of patients and correlates with other published findings.\(^{113}\)

All patients who undergo ACEI renal scintigraphy have their BP measured routinely in the DNM on the day of the scan (in addition to serial measurements following ACEI administration). Based on the BP measurements taken in the DNM (independent and irrespective of the referring physician indicating the severity of BP on the request form), 42 (30%) patients were found to have severely elevated SBP and 28 (20%) had severely elevated DBP. The severity of the BP in the majority of patients with severe hypertension was not mentioned on the request form and was found on routine BP measurement in the DNM. This reemphasises the need to do independent and routine BP measurements in all patients referred for ACEI renal scintigraphy irrespective of what is stated on the request form to ensure that a patient with severe hypertension is not missed.

Furthermore, severe hypertension could be used as a clinical correlation for a positive ACE inhibitor study (improving the reader’s diagnostic confidence that one is dealing with a true positive study). Lastly, this finding indicates the need to educate referring physicians about the importance of severe hypertension as an important predictive criterion for RVH.

5.4.4 Abdominal bruit

3 patients (2.1%) were found to have abdominal bruit, but only one (0.7%) had a positive renography. The presence of abdominal bruit should be pathognomonic of RVH but, in this study, the findings were not in keeping with literature which states that the presence of abdominal bruit is associated with high incidence of RVH. A significant number of abdominal
bruit may have been missed because it requires an experienced clinician to elicit the sign of an abdominal bruit.

5.4.5 Grade 3 and 4 retinopathy

One (0.7%) patient was said to have grade 3 and 4 retinopathy and that particular patient had positive renography, which further validates the presence of retinopathy to be reliably associated with RVH.

5.4.6 Refractory hypertension

Five patients (3.6%) had refractory hypertension and none of those had a positive renography.

5.4.7 Patients with unspecified indication

A large number of referrals (48/140=30.1%) was seen for patients whose indications did not meet the criteria according to the EANM guidelines. 2 (1.4%) had positive renography. Among the two, 1 patient (0.7%) had presented with severe hypertension, which was not stated as a reason for referring the patient.

The rest of the criteria, such as unexplained azotaemia, worsening in renal function, onset of hypertension after the age of 50 years, pulmonary oedema and umbilical catheterisation had no representations as far as data collection was concerned.

5.5 The negative results in relation the blood pressure

A total number of 130 patients had negative results and amongst those, the majority of patients (43 cases (33.1%)) had a normal DBP, while 25 (19.2%) had severely elevated DBP.

With respect to SBP, most patients (47 cases (36.2%)) had a moderately elevated SBP and 35 (26.9%) had severely elevated SBP.

The majority of patients with a negative ACEI renal study did not fall into the severe category for neither SBP nor DBP readings (as opposed to the patients with positive studies). The results are however not statistically significant and BP readings can therefore cannot be used alone to confirm a negative result.
5.6 ULTRASOUND

Ultrasonography did not form part of the research protocol but was, in hindsight, part of the data collection. The results showed that 99 patients (70.7%) did not have ultrasonography done prior to captopril renography and 41 (29.3%) had benefitted from ultrasonography. Among those who had ultrasonography done, 17 (41.4%) had abnormal results and 26 (63%) had normal results. Among the 10 patients with positive renography, five (50%) patients were found to have abnormal ultrasonography reports. This result yields a good correlation between ultrasonography and renography. It imperative to highlight that, although the number of positive ultrasonography reports was high (17) when compared to positive scans seen on scintigraphy (5/10), the stenosis found on ultrasonography must be haemodynamically significant in order to be detected on an ACEI renography.

5.7 RADIOPHARMACEUTICALS

A significant number of patients 98 (70%) were imaged using Tc-99m DTPA, while 42 (30%) were imaged using Tc-99m MAG3. The current results are in keeping with evidence that Tc-99m DTPA is the preferred radiopharmaceutical for imaging patients with suspected RVH. The rationale is based on the fact that Tc-99m DTPA is less dependent on hydration in that the amplitude of the curve and its differential function of the kidneys are the most important diagnostic criteria. Tc-99m MAG3 depends on the hydration status of the patient and the use of diuretics. In our centre, the choice of using Tc-99m MAG3 is commonly influenced by the presence of children or patients with renal failure on that particular day. Out of the 10 positive scans, 8 (80%) were done using Tc-99m DTPA and 2 (20%) were done using Tc-99m MAG3.

5.8 CONCLUSION

Audits in Nuclear Medicine are good quality control measures that help in improving the services rendered by the unit. It is therefore important to follow the recommended guidelines in order to maximise cost effective and streamlined use of the services offered by the DNM.

This audit reveals that the majority of patients with suspected RVH, who were referred for ACEI renal scintigraphy at the DNM at DGMAH, were not thoroughly screened for the study as per the criteria specified in the EANM guidelines. Given the cost and radiation exposure associated with ACEI renal scintigraphy, performing the study without adequate pre-test justification (as per the defined criteria) results in the inappropriate performance of the exam.
The fact that the overwhelming majority of patients in this retrospective series presented with a negative study further highlights the need to apply the defined EANM criteria to justify the judicious use of resources.

5.9 LIMITATIONS AND RECOMMENDATIONS

5.9.1 Limitations

Patients’ files which were missing or had missing information due to a transition from paper to paperless system formed part of the drawbacks to the study – the missing data from these patients may have improved the overall confidence of the study by increasing the number of participants. This problem will, however, be overcome in future by the PACS (picture archiving and communication system) which was installed in September 2016.

The small number of positive studies did not allow for significant statistical analysis – this was beyond the control of the researcher as a prediction of the number of positive studies could not be determined at the beginning of the retrospective data collection.

The retrospective series and findings involved patients at a single institution and cannot be necessarily extrapolated to other centres.

The study design did not include ultrasound and or CT angiography in the data collection instrument, but did mention it in the discussion (in the limited number of patients where it was available) – correlative imaging is important as it increases diagnostic confidence.

5.9.2 Recommendations

Based on the findings of this retrospective study, the following recommendation are suggested:

- Continuous medical education (CME) for referring physicians is required.
  - They need to be made aware of the criteria defined in the EANM guidelines prior to referring a hypertensive patient for ACEI augmented renal scintigraphy in order to justify the cost and radiation exposure to the patient.
  - CME could be in the form of formal lectures delivered on a regular basis and physician information leaflets/posters to be distributed in out patient clinics and wards.
- A ‘vetting form’ (attached as appendix 2) has been designed to further and more effectively screen patients referred for ACEI renal scintigraphy.
- Correlative imaging (ultrasound and CT angiography) should also form part of the work up of a patient with suspected RVH. A protocol should be developed in conjunction with the radiology department.
6. REFERENCES


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CHAPTER 7

APPENDICES

7.1 Data extraction form

SECTION A; PATIENT DERMографIC DATA

- NAME (initials only) ………………
- NUCLEAR MEDICINE NO ……………
- GENDER …………………………
- AGE (years) ………………………
- STUDY NO ………………………

SECTION B: CLINICAL DATA

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<tr>
<th></th>
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</thead>
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<td></td>
</tr>
<tr>
<td>Severe hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal bruits</td>
<td></td>
<td></td>
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<tr>
<td>Unexplained azotemia in elderly patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening renal function in patients on ACEI</td>
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<td></td>
</tr>
<tr>
<td>Grade 3 or 4 retinopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset before 30 or after 55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
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<td>Hypertension in infants an umbilical artery or catheter</td>
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SECTION C: FINDINGS/RESULTS

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</table>
7.2 Vetting form for renovascular hypertension

Dr. George Mukhari Hospital

Department of Nuclear Medicine

P.O Box 83, Sefako Makgatho Health Sciences University, 0204, South Africa

Tel: (012) 521 5865/5821, Fax (012) 521 4604, Email: marlize.viljoen@smu.ac.za

VETTING FORM FOR RVH REQUESTS

(Incomplete form will result in rejection of request)

Patient------------------------------------------- Referring Doctor ----------------------------------------

---------------------

Date of request: -------------------------------Doctors contact detail: ----------------------------------

-------------------

Yes (x)/ No (x)

History:

(At least one or more clinical finding must be present in a patient)

Onset of hypertension before the age of 30

Onset of hypertension after the age of 30

Severe hypertension

Refractory hypertension

Abrupt onset of hypertension

Abdominal bruit

Worsening renal function on ACEI

Grade 3 or 4 retinopathy

Umbilical catheterization

Hypertension in children
Current clinical findings:

- Systolic: SBP of more than 140mmHg
- Diastolic: DBP of more than 100mmHg

Medication:

ACE inhibitors
Diuretics
Calcium channel blockers

Related investigations:

- Urea and electrolytes
- Renin levels
- Doppler ultrasound
- CTA

Vetting Doctor at Department Nuclear Medicine

-----------------------------------------------
7.3 Ethical clearance certificate

Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee (SMUREC)

Molotlegi Street, Ga-Rankuwa 0208
Tel: (012) 521 5817/3698 | fax: (012) 521 3749
Email: lorato.phiri@smu.ac.za
P.O. Box 163 Medunsa 0204

APPROVAL NOTICE - NEW APPLICATION

06 August 2015

Dr PB Nemutaduni
Department of Nuclear Medicine
P.O Box 63
Medunsa, 0204

MEETING:

SMUREC Ethics Reference Number:
SMUREC/M/180/2015: PG

The New Application received on 02 July 2015, was reviewed by members of Sefako Makgatho University Research Ethics Committee on 06 August 2015 and was approved on 06 August 2015.

Title:
An audit of compliance to referral criteria for patients with suspected renovascular hypertension referred for angiotension converting enzyme inhibitor study at Dr George Mukhari Academic Hospital

Researcher:
Dr PB Nemutaduni

Supervisor:
Dr AA Gutta

Co-supervisor:
Prof T Mdaka

Hospital Superintendent:
Dr Sithole (DGMAH)

Department:
Nuclear Medicine

School:
Medicine

Degree:
MMed Nuclear Medicine

Please note the following information about your approved research protocol:

Protocol Approval Period:
06 August 2015 – 06 August 2016

Please remember to use your protocol number (SMUREC/M/180/2015: PG) on any documents or correspondence with the REC concerning your research protocol.

Please note that the REC has the prerogative and authority to ask further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.

International Organisation (IORG0004315), Institutional Review Board (IRB00085122), Federal Wide Assurance (FWA00069419)

Expire date: 11 October 2016 and WIHREC No: REC 216408-003

Sincerely,

[Signature]

PROF GA GUNUNJAO
CHAIRPERSON SMUREC

[Stamp]